Discussion

Section E1: Knowledge gaps in causation of cancers : Progress made and further research needs

In their seminal work on the epidemiology of cancer, Doll and Peto (1981) estimated that about 80% of cancers have an identifiable cause related to lifestyle or environment. This estimate was derived essentially from the observation of considerable between-country differences in specific-cancer mortality and in lifestyle and environment.

In contrast to their evaluations, we conclude that in France in the year 2000, non-hereditary risk factors were identified for only around 50% of cancers in men and around 26% cancers in women (see Section C1). Other studies, based on approaches similar to the one adopted in this report, yielded results on attributable fractions of cancer for the Nordic countries and for the world (Olsen et al., 1997, Danaei et al., 2005) that were quite similar to those we found. Hence, a specific "cause" cannot be identified for a majority of cancers. This is not surprising in view of the insufficiency of our knowledge of carcinogenesis.

Since the 1950s, considerable means have been devoted to the identification of causes of cancer and the study of carcinogenesis, notably in the USA. The programme "Europe Against Cancer" of the European Commission from 1985 to 2000 succeeded in raising concerns about cancer causation and ways to control the disease in Europe. Huge progress in the understanding of carcinogenesis has been made, but these advances have raised new problems.

About 2–4% of cancers have an established genetic origin, being due to known mutations associated with higher cancer risk. However, genetic epidemiology and studies on twins (Lichtenstein et al., 2000) suggest that the hereditary component is greater. For instance, for breast and ovarian cancer, besides carriers of mutations in the BRCA1 and 2 genes, there is a notable proportion of familial cancers in which these genes are not mutated. In other types of cancer too, mutations of known genes are not sufficient to account for all hereditary factors (Kony et al., 1997). Considerable funds and energy have been devoted in the 1990s and 2000s to finding other variations in the genetic code and its expression in order to define the contribution of hereditary factors to the probability of cancer occurrence; but this is a long-term endeavour.

The aim of this section is to show that, despite the limitations of our current knowledge, recent advances in cancer biology are already sufficient to help in interpreting the epidemiological data. Carcinogenesis is such a large field of research that we shall not attempt to cover all of it. However, in order to put into perspective the epidemiological data, many of its facets merit discussion.

1. Carcinogenesis: a complex multi-step process

1-1 Complexity of carcinogenic processes

During the past two decades, new data have demonstrated that carcinogenesis is a far more complex process than previously suspected (Pitot and Dragan, 1994; Vogelstein and Kinzler, 1993, 2004; Ito et al., 1995; Trosko, 1997; Sjöblom et al., 2006; Sonnenschein and Soto, 2000; Tubiana, 2007) and research has focused on several new problems such as the role of reactive oxygen species (ROS) in DNA damage (Spitz et al., 2004), immunosurveillance,

and the defences against mutation and appearance of aberrant cells at the level of the cell, the tissue and the microenvironment. It is now recognized that cancer is not caused simply by the transformation of one cell, but also involves the reactions of the microenvironment and the tissue (Averbeck et al., 2006, Averbeck, 2007; Hanahan and Weinberg, 2000; Hahn and Weinberg, 2002; Park et al., 2003).

Berenblum and Shubik (1947) were the first to distinguish, through their experiments on the skin of rodents, two steps during carcinogenesis: *initiation*, which is caused by a genotoxic agent (the one they used was 7,12-dimethylbenz[a]anthracene (DMBA), and promotion, which was associated with the local application of croton ester oil or mechanical irritation. Mutations caused by genotoxic agents generally remain occult in the genome until a promoter agent is applied. In experimental animals, the time interval between initiation and promotion can be very long, which suggests that initiation is an irreversible step, probably linked to DNA damage in the stem cells. On the other hand, the interval between promotion and emergence of an invasive cancer is relatively constant. Observations in humans are consistent with experimental data. The interval between initiation and emergence of an invasive cancer can be very long. For example, following the atomic-bomb explosions over Hiroshima and Nagasaki, an excess of breast cancer was observed; but irrespective of the age at irradiation, the breast cancers in irradiated women were detected at the same age as in non-irradiated women. However, the excess of breast cancer is much greater when the age at irradiation is young (around age at menarche).

In the 1960s, *progression* was recognized as a third main step.

Armitage and Doll (1957) analysed the relationship between age and occurrence of cancer and concluded that cancer was due to accumulation in the genome of a single cell of 6 to 10 specific genomic damages. They thought that many of the events were occurring by chance and that carcinogenesis was a stochastic process. Later it was shown that the probability of such accumulation was extremely small in normal circumstances (Brash, 1997), but can be enhanced by several mechanisms (see Section 1-3-2).

1-2 The role of reactive oxygen species (ROS) in initiation

Aerobic living organisms have existed for at least 2.5 billion years. During oxygen metabolism, ROS are produced which are potent genotoxic agents (Burcham, 1999; Hsie et al., 1986; Guyton and Kensler, 1993; Klaunig et al., 1997; Feinendegen, 2002; De Bont and van Larebeke, 2004; Barnes and Lindahl, 2004). About 95% of molecular oxygen is converted into carbon dioxide and 5% into ROS (Barber and Harris, 1994). These ROS cause much DNA damage each day in each cell (Burkart et al., 1999, Cadet et al., 2004): about 55 000 single strand breaks, 8 double strand breaks (the most deleterious damage) and many other types of DNA damage.

The amount of DNA damage caused each day by ROS is similar to that induced by a radiation dose equal to 200 mSv per day (Burkart et al., 1999). During oxidative stress, which can be induced by several types of aggression, such as an infection or strenuous physical exercise (Dent et al., 2003; Bakkenist and Kastan, 2004), the number of ROS, and the resulting extent of DNA damage, can be much higher. DNA is a fragile macromolecule. Aerobic organisms would not have survived without effective repair mechanisms. Cell defences are activated during oxidative stress and they include: (i) the synthesis of anti-oxidant molecules (such as glutathione) and enzymatic systems which destroy ROS (such as catalase or superoxide dismutase, SOD), (ii) DNA repair, (iii) in multicellular organisms, since their appearance about 500 million years ago, control or elimination of mutant cells, which plays a crucial role in protecting the organism (Averbeck et al., 2006; Averbeck, 2007; Chandra et al., 2000).

1-3 Defence mechanisms

1-3-1 DNA repair. Most of the DNA repair systems present in mammalian cells existed already in yeast 800 million years ago, but have become more sophisticated during evolution. Almost nothing was known about DNA repair in 1980, but this has since become one of the main topics of cell biology research. It involves sensor molecules which constantly monitor DNA molecules. When a certain amount of damage is detected, signalling systems are triggered (e.g., the intranuclear ATM and ATR signalling systems), which

arrest cell progression and may activate DNA repair mechanisms, or apoptotic pathways (Averbeck et al., 2006; Averbeck, 2007, Bakkenist and Kastan, 2003; Christmann et al., 2003; Hoeijmakers, 2001; Jeggo and Lobrich, 2006; Sancar et al., 2004).

In a mammalian cell, several thousand genes are devoted to protecting the genome. Defects in the DNA repair systems are associated with much higher cancer incidence. For example, xeroderma pigmentosum is a disease in which DNA repair mechanisms following irradiation by solar ultraviolet rays are impaired. In these patients, the incidence of skin cancer is dramatically increased.

Most mutations are not caused by a genotoxic agent but are due to errors during DNA repair. These errors are very infrequent when the amount of cell damage is small, but their incidence increases markedly when the amount of DNA damage simultaneously present in a cell becomes greater, because the repair mechanisms then become more error-prone (Dikomey and Brammer, 2000); however, even when the amount of damage is limited, misrepair can occur.

Most genes that are associated with an increase in cancer incidence (for example, *BRCA1* and *BRCA2* in breast cancer) are genes that are involved in repair mechanisms and/or in cell progression throughout the cell cycle.

1-3-2 Elimination by death of cells with DNA damage

Elimination of cells with altered DNA plays a crucial role that was long overlooked (Guo and Hay, 1999; Sancar et al., 2004; Shiloh, 2003; Académie des Sciences – Académie de Médecine, 2005; Columbano et al., 1996; Chandra et al., 2000; Hickman, 2002).

When the amount of DNA damage in a cell is small, intranuclear signalling mechanisms may not be triggered and the cell dies (Rothkamm and Löbrich, 2003; Collis et al., 2004). Apoptosis, and other types of programmed cell death, eliminate cells with altered DNA or ones in which DNA damage has not been properly repaired, as well as aberrant cells of other types (Hickman, 2002; Schulte-Hermann et al., 1995).

A defect in apoptosis is a crucial step in carcinogenesis because it allows (i) the accumulation in the same cell of a large number of mutations and (ii) clonal amplification of the abnormal cells (Brash, 1997). The TP53 gene has a critical role in apoptosis and in the orientation of cells with DNA damage towards either DNA repair or apoptosis. It is mutated in over half of human cancers (Flores et al., 2002; Guo and Hay, 1999).

Apoptosis is not activated when the proportion of cells with DNA damage is too high, perhaps because it would dangerously enhance tissue injury (Académie des Sciences - Académie de Médecine, 2005).

1-3-3 Senescence, or loss of proliferation potential, is an alternative pathway for avoiding the transmission by a somatic cell of genetic defects to daughter cells. It is programmed and its importance has been recently underlined (Campisi, 2005; Schmitt, 2007).

1-4 Cancer initiation

As the first step towards carcinogenesis, initiation of cancer is linked to damage to the genome of a single cell (i.e., the monoclonal origin of human cancers) that succeeds in escaping the numerous control mechanisms preserving genomic integrity and tissue structure (Hanahan and Weinberg, 2000). It corresponds to a mutation conferring on a cell the ability to proliferate without a signal from a growth factor (for instance, when a proto-oncogene becomes an oncogene). All genotoxic agents, endogenous (such as ROS) or exogenous (such as solar ultraviolet radiation or ionizing radiation), can cause initiation.

Several broad types of mechanism can contribute to the accumulation of genomic damage possibly leading to cancer:

(i) *Genetic instability,* that is a greater propensity to accumulate DNA damage because of defects in DNA repair systems or because of a variety of mechanisms which induce chromosomal defects (e.g., aneuploidy) (Bjerkvig et al., 2005; Morgon, 2003; Li et al., 2001).

(ii) *Cell proliferation:* many human carcinogenic factors stimulate cell proliferation (for example, hormones, alcohol, energy-rich diet, and factors causing irritation, e.g., tobacco smoke). Greater cellular proliferation means higher numbers of mitoses that increase the likelihood of genomic defects (Ames and Gold, 1990; Cohen and Ellwein,

1990; Moore and Tsuda, 1998; Columbano et al., 1996).

(iii) *Amplification of subclones with apoptotic defects:* Normally, a cell that has incurred irrecoverable DNA damage (e.g., caused by a genotoxic or a mutagenic agent, but also by an error during mitotic processes) is self-eliminated by apoptosis. However, mutation (with inactivation) of critical genes implicated in cell-cycle regulation (e.g., the TP53 gene) and defects in apoptosis may allow the proliferation of cells that have accumulated DNA defects (Brash, 1997).

1-5 Promotion

The proliferation of initiated cells is generally prevented by the constraints exerted by the normal surrounding cells, the microenvironment and the tissue (Barcellos-Hoff, 2005; Tubiana 2007). There are many promoters that may overcome these constraints: endogenous (hormones such as estrogen for mammary cells, growth factors, etc.) or exogenous (alcohol, mechanical irritation, etc.). Inflammation and infections also have promoting effects (Takahashi et al., 2000). The proliferation rate reverts to normal when the promoter agent ceases to be present, unless a sub-clone has appeared that can proliferate without a promoter. The appearance of such a sub-clone marks the end of the promotion phase and opens the third phase of progression.

Promotion can also be caused by agents that alter intercellular communication such as phorbol esters. Foreign bodies such as asbestos can also perturb intercellular communication and may be carcinogenic through this mechanism (Klaunig, 1991; Rosenkranz et al., 2000; Yamasaki et al., 1995; Brand, 1982; Trosko et al., 2004).

1-6 Extracellular defences against carcinogenic processes

The development of an invasive cancer is opposed by defence mechanisms at the levels of microenvironment, tissue and body. At the tissue level, neighbouring cells control each other's proliferation (e.g., the role of cytokines) (Radisky and Bissell, 2004; Bhowmick et al., 2004; Barcellos-Hoff and Ravani, 2000; Barcellos-Hoff, 2005; Kalluri and Zeisberg, 2006; Liotta and Kohn, 2001). These mechanisms are probably similar to those active in embryogenesis and in tissue regeneration following an insult (Derksen et al., 2004; Giles et al., 2003; You et al., 2002; review in Beachy et al., 2004). Cancerous cells can not only overcome but also manipulate protective mechanisms, in order to be recognized as "friend" instead of being fought as "foe" (Mueller and Fusening, 2004). Many factors, such as infection and inflammation (Christen et al., 1999; Modugno et al., 2005), may contribute to enhancing cell proliferation of potentially malignant clones, facilitating the emergence of a clone of fully transformed cells.

Tissue disorganization, such as that caused by the death of a large number of cells or impairment of cell interactions, may facilitate the escape of potentially malignant cells from the tissue control system (Park et al., 2003). Tissue disorganization through disease also facilitates the escape of a sub-clone from the barriers of the microenvironment (Clark, 1995; Barcellos-Hoff and Ravani, 2000; Barcellos-Hoff, 2005). For example, liver cirrhosis facilitates the occurrence of a liver cancer; lung fibrosis (due to silicosis or asbestos) or chronic bronchitis (associated with tobacco) facilitate the occurrence of a lung cancer. Large amounts of any genotoxic agent, physical or chemical, kill a high proportion of normal cells and therefore induce proliferation by a compensatory homeostatic mechanism.

A promoting effect can also be caused by repeated exposure to a mutagenic agent; thus, chronic exposure to solar ultraviolet induces clonal amplification of sub-clones with an apoptosis defect (Brash, 1997).

1-7 Progression

During this last phase of carcinogenesis, preneoplastic cells become progressively more malignant, because during proliferation new mutations can occur and can originate new sub-clones (Cahill et al., 1999). Progression continues when the tumour has become an invasive cancer and increases its malignancy.

At the body level, immunosurveillance has the ability to control cancer progression, but when a cancer is clinically detectable, this is because the immune mechanisms have been overcome (Pardoll, 2001). Nevertheless, they can still be exploited in therapy (Taieb et al., 2006). Immunodepression

increases the incidence of several cancer types (Euvrard et al., 2003). Still at the body level, proteins can control or promote angiogenic phenomena and thus contribute to the inhibition or facilitation of the invasive properties of tumours arising in the organism (Folkman and Kalluri, 2004).

1-8 Genes involved in cancer

The sequencing of the human genome has paved the way for new avenues of research. Sequencing of DNA extracted from human tumours has revealed that the number of genes involved in carcinogenesis may be greater than previously assumed (Cancer Genome Atlas Project). The search continues for new genes or polymorphisms which may enhance the interaction between carcinogenic agents and the genome. Recently, it has been shown that about 300 micro-RNAs are present in the genome. They modulate the expression of several genes and their mutation or abnormal expression appears to affect carcinogenesis (Esquela-Kerscher and Slack, 2006; Thompson et al., 2006).

The existence of stem cells in tumours is now recognized (Monier, 2007) and it is highly probable that most human tumours derive from normal stem cells or progenitors. After DNA damage, stem cells may be more prone to apoptosis than to DNA repair (Cairns, 2002).

Some biological mechanisms implicated in cancer occurrence may not be directly related to DNA lesions, but to mechanisms mimicking DNA lesions or to events taking place in the cytoplasm and thus not requiring DNA lesions (Li et al., 2001). These mechanisms include epigenetic events such as DNA methylation and metabolic functions within and between cells, involving complex proteins and enzymatic functions.

Epigenetic phenomena are a growing field of cancer research (Baylin and Ohm, 2006; Gaudet et al., 2003; Konishi and Issa, 2007; Widschwendter et al., 2007; Schlesinger et al., 2007; Klochender-Yivin et al., 2002). They affect the expression of genes and the chromatin structure and play an important role in carcinogenesis. The occurrence of epigenetic phenomena involved in cancer is progressive and is not the result of stochastic processes.

Clearly, the previous concept which associated carcinogenesis with the mutation of a limited number of genes in one cell is no longer tenable (Trosko, 1997; Sjöblom et al., 2006). New concepts that have emerged during the past decade should have an impact on both the strategy of cancer prevention and the understanding of dose–carcinogenic effect relationships.

1-9 Interactions between endogenous and exogenous carcinogenic agents

Endogenous and exogenous carcinogenic agents are often intermingled during carcinogenesis, the exogenous being able to increase the probability of a cancer occurrence. However, a cancer can be caused by endogenous factors without the intervention of exogenous agents. Breast cancer, for example, is associated with exposure of mammary cells to sexual hormones and its incidence is much lower after an ovariectomy, which suppresses hormonal secretion (Rochefort, 2007). Conversely, the administration of estrogen for alleviating the symptoms associated with menopause increases breast cancer incidence by about 10% (Section B7). Thus one should not treat endogenous and exogenous factors as independent. In cancer prevention, both should be considered, but their respective roles vary with the type of cancer, lifestyle and environmental factors. 95% of lung cancers are due to tobacco and the same proportion of upper respiratory and upper digestive tracts cancers are due to the association of alcohol and tobacco. However, in the early 1960s in France among women, the proportion of lung cancer associated with tobacco was less than 30% because in 1945 most women did not smoke.

1-10 Examples of complexity of carcinogenic processes

Examples of the complexity of carcinogenic processes are numerous: for instance, in the lung, tobacco smoke is both a mutagenic factor and a source of chronic irritation and infection which enhances cell proliferation and tissue disorganization (Tubiana, 1999; Hazelton et al., 2005). The rapid decrease in lung cancer incidence after cessation of tobacco smoking underlines the prominent role of irritation and infection (even more rapid decreases in cardiovascular events are observed after smoking cessation, also linked to changes in inflammatory

phenomena in blood vessels).

Asbestos is a potent carcinogenic agent. Yet it is neither genotoxic nor mutagenic. The mechanism by which it causes genomic aberration is open to question and may simply involve tissue disorganization and interference with communication between cells (Brand, 1982).

In Africa, Burkitt lymphoma is due to the Epstein-Barr virus, but viral infection can lead to a clinical cancer only if an infant has been contaminated at a young age and if the body defences have been weakened by malaria (see Section B3). Burkitt lymphoma tends to disappear in African regions where malaria has become less common over time.

1-11 Summary

It now appears that while alteration of the genome of an initiated cell is a key event in carcinogenic processes, it is far from being sufficient to induce a cancer. Promotion could be more important. Currently, our insufficient understanding of the complexity of biological processes involved in carcinogenesis leads to difficulties in formulating hypotheses for the search for etiological factors. Cancer is caused not only by a mutation and the appearance of a neoplastic cell. It is also, and possibly mainly, a disease of the tissue, the microenvironment and intercellular communication.

2. Carcinogenic processes and cancer occurrence

The great complexity of carcinogenetic processes strongly suggests that a mutation in a cell has a very small likelihood of inducing an invasive cancer.

Among women with a mutated *BRCA1* or *BRCA2* gene, only about 50% will develop a breast cancer, although all mammary cells carry this defect (about 20 billion mammary cells, among which are about 200 million stem cells). These numbers show that the induction of such a mutation in a single cell has a very low (about 10-8) probability of inducing a breast cancer, even in a stem cell. This suggests that a small increase in the number of cells in which a mutation has been induced in a gene involved in the carcinogenic process can increase, but only modestly, the probability of cancer occurrence.

This conclusion is consistent with epidemiological data showing that promoters (hormones, alcohol) induce many more cancers than small doses of genotoxic agents. However, it should be recalled that high doses of genotoxic agents provoke cell proliferation and have a promoter action.

Another significant recent discovery is the long latent delay that can occur between an initiating event and the appearance of cancer induced by this event. For example, sixty years after the atomic bomb explosions in Japan, the incidence of colon cancer is still increased, slightly but significantly. Thus in the search for causes of cancer, more studies should be focused on risk factors during infancy, childhood and adolescence. Recent data revealing an association between the characteristics of a newborn and the probability of breast cancer fifty years later (Vatten et al., 2005) should encourage more investigation concerning gestation and infancy.

3. Dose–carcinogenic effect relationships and the effect of low doses

3-1 Assessing the carcinogenic effects of low doses

Assessment of risks associated with low-dose exposures has been one of the most controversial issues in oncology in recent years (Abelson, 1994; Ames and Gold, 1990, 1997). The inability of epidemiological surveys to detect evidence of a carcinogenic effect linked to low doses may be due to the insufficient statistical power of the studies, but also shows that the carcinogenic effect, if it exists (which is still debatable), is likely to be very small.

From a biological point of view, our current knowledge is compatible with the existence of a threshold (Académie des Sciences - Académie de Médecine, 2005; Feinendegen et al., 2007). Cells react efficiently to internal and external stresses. The various safeguard mechanisms protect the genome, to ensure the maintenance of genetic stability and to eliminate aberrant cells (see Section E1.1-3). The same types of complex systems of response and homeostatic regulation operate for aggression by endogenous (ROS) or exogenous (UV, ionizing radiation, chemical mutagens) agents. These systems encompass both repair of damage and prevention of further damage. But the main fact is that low doses of a genotoxic agent (for example, ionizing radiation) initiate biological responses that differ from those

observed at higher exposure. Low doses induce a delayed appearance of temporary changes in cellular signalling affecting intracellular enzyme activities, reactions to ROS, DNA repair, apoptosis, cell differentiation, and adaptive and immune responses (Feinendegen et al., 2007). These changes include a killing effect of preneoplastic cells (Portess et al., 2007), which may temporarily decrease the cancer incidence. The existence of a hormetic effect has long been debated but is now recognized, at least for experimental animals (Azzam et al., 1996; Calabrese, 2004). Adaptive responses show that when alerted by a challenge dose, cells can become more resistant to genotoxic agents (Wolff et al., 1988; Wolff, 1998; Rigaud and Moustacchi, 1996; Day et al., 2007, Tapio and Jacob, 2007).

Other phenomena, such as variations in mutations or carcinogenic effects with dose rate (Vilenchik and Knudson, 2000, 2006), modifications of phospho-proteome profiling in response to low or high doses of irradiation (Yang et al., 2006), low-dose hypersensitivity, and bystander effects (Mothersill and Seymour, 2006), confirm that responses to radiation (UV or ionizing) are modulated by dose. Indeed, activation of anti-oxidant defence, gene induction, DNA damage and signalling clearly differ at low or high exposure levels. Moreover, modern transcriptional analysis shows that the genes which are activated or repressed are not the same following a low or a high dose (Amundson et al., 2003; Franco et al., 2005). Moreover, the chronology of responses is different (Franco et al., 2005). Passive smoking is often quoted as an example of an agent that is carcinogenic at low doses. This conclusion is debatable. Passive smoking corresponds to 1 to 2 cigarettes smoked per day, that is, about 500 cigarettes per year, corresponding to a few grams of tar per year. This is far from being a low dose.

3-2 Extrapolations from carcinogenic effects of high-doses

Carcinogenic effects of low doses or concentrations of physical or chemical agents are generally estimated by an extrapolation based on a dose–effect relationship. The most widely used is the linear no-threshold (LNT) relationship, based on the assumption that (i) even the smallest dose of a carcinogen can cause a mutation which may initiate the carcinogenic process, (ii) the probability of initiation (per unit dose) is constant, irrespective of the dose, dose-rate or concentration, an assumption that is debatable because the efficacy of cell defence decreases with greater local time and spatial density of the damage (Dikomey and Brammer, 2000), and (iii) after the initiation of a cell, the carcinogenic process evolves similarly whatever the number of damaged cells in the microenvironment or the tissue. The discussion above (Section E1.1-3) shows that recent data are not consistent with these three assumptions.

Views opposing the LNT hypothesis have been expressed (Abelson, 1994; Ames and Gold, 1997; Feinendegen et al., 2007; Tubiana et al., 2006a,b; Yamamoto et al., 1998). Pasteur, 125 years ago, showed that inoculation of a small amount of micro-organisms can “vaccinate” against subsequent inoculations of large amounts of the same micro-organism. Adaptive responses that occur following an aggression by low doses of a genotoxic agent may correspond to a similar type of protective mechanism operating by a temporary up-regulation of defences (Feinendegen, 2007; Wolff et al., 1988; Wolff, 1998).

Currently, most regulations regarding carcinogens are based on the LNT relationship, despite its uncertain validity. In radioprotection (see Section D1), for example, the philosophy of the current recommendations is that there is no innocuous dose. Rather than defining a safe dose, this concept leads to the need to define what amount of risk is acceptable to society.

The joint report of the two academies (Académie des Sciences - Académie de Médecine, 2005) pointed out the drawbacks of the LNT hypothesis and its limitations. The absence of epidemiological data for low doses does not allow us to conclude that such doses have no carcinogenic effect but neither does it justify the use of LNT. For most carcinogens, the existence of a threshold is plausible due to the efficacy of defence mechanisms in the low dose range. In such cases, the use of LNT is not recommended because its drawbacks (the anxiety raised by risk overestimation and the cost of protective measures) can be greater than the advantages of the precautionary approach.

With regard to promotion or to epigenetic processes, LNT is even less scientifically plausible (Trosko, 1997). The existence of a threshold is highly probable when the carcinogenic agents are non-genotoxic promoting factors and for factors which

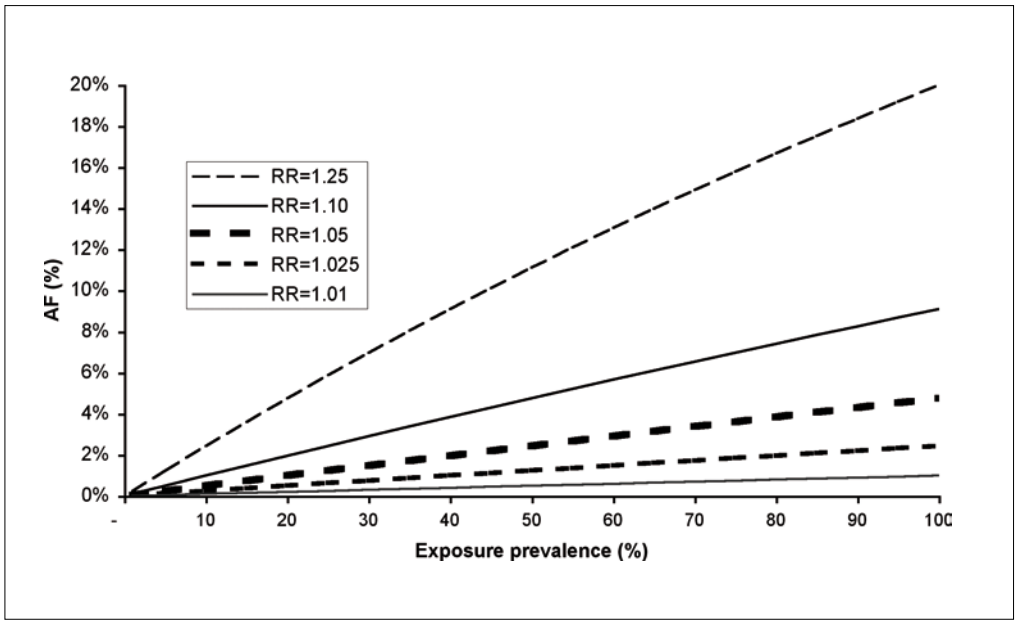
induce epigenetic transformation, but a threshold may also exist for genotoxic agents.

3-3 Statistical considerations on effects of low doses

A carcinogenic agent may be associated with a low relative risk of cancer (say, RR < 1.25) if exposure to that carcinogenic agent is limited to low doses. In the absence of a threshold and if a large proportion of the population is exposed to such low doses, a low risk factor could nevertheless have a low but observable impact on cancer incidence in the population. Figure E1.1 plots AFs according to exposure prevalence and for various levels of RR associated with exposure to low doses of a hypothetical carcinogenic agent. If the excess risk is less than 10% (i.e., RR = 1.10), then even if all the population were exposed to the agent, less than 10% of cancer would be due to that agent. It is only if the RR is higher that the proportion of cancer attributable to the agent increases substantially.

Because studying the effect of low doses poses formidable problems in epidemiology, most low-dose effects are derived from mathematical models that more or less assume that the type of risk factor–cancer relationship at low doses is similar to the relationships observed with medium and high doses. As previously discussed, this assumption is debatable for a number of reasons. Nevertheless, for some risk factors, low doses could theoretically be associated with specific effects on some biological events, including cancer, for instance, a chemical substance with hormone-like activity when acting at low dose on specific receptors, or hormones that have different types of biological activity at low and at higher concentrations (e.g., the so-called hormone-disruptors). The latter phenomenon, however, has never been observed in epidemiological studies and remains highly hypothetical.

Figure E1.1 - Attributable fraction of cancer to an agent in case of low RR



4. Not all cancers have an identifiable non-genetic cause

Exogenous genotoxic agents play a role in cancer by increasing the number of mutations, but, as previously discussed (Section E1.1-8), cancer initiation can occur without exogenous risk factors. Hence, for many cancers, it is probably illusory to expect to discover a specific causal factor explaining their occurrence.

Ageing is the main determinant of the incidence of several major cancers (e.g., colorectal cancer, prostate cancer). With ageing, a steadily greater proportion of cancer may not be due to specific exogenous causes, but rather to the probability that ageing cells accumulate biological "damage" or "errors", possibly leading to carcinogenic processes. Another possibility is less effective immunosurveillance.

5. Diet and nutritional factors

The most compelling evidence for a role for diet and nutritional factors in cancer occurrence comes from epidemiological studies of migrants and of declining stomach cancer incidence.

Migrant studies show that subjects moving from areas with a low incidence of several cancers, including colorectal and breast cancer, tend to acquire the cancer incidence levels of the host populations (e.g., Tomatis et al., 1990; McCredie et al., 1999, Maskarinec and Noh, 2004). This observation led to the hypothesis that nutrition was the predominant factor responsible. However, other factors than nutrition could also be involved (e.g., changes in reproductive factors in women, although this explanation cannot be evoked for colorectal cancer).

The dramatic decline in stomach cancer over the past 50 years in most industrialized countries is deemed to be partly due to changes in food preservation (e.g., refrigeration instead of salting or smoking) and nutritional habits (e.g., greater availability of fresh fruits and vegetables). A decline in *Helicobacter pylori* colonization of the stomach due to antibiotic treatment for other diseases or specific eradication of this bacterium has probably also contributed to the decrease in the stomach cancer burden (Tomatis et al., 1990).

Uncertainties about the role of nutritional factors arise from the apparent inability of epidemiological studies to identify critical nutrients or dietary patterns associated with cancer risk (Roe, 1979; Kolaja et al.,1996). Several new avenues being explored are outlined below, and new epidemiological and experimental studies are needed to examine the relevance of these concepts.

(i) Most prospective studies and interventional trials on nutrition and cancer have been performed in adults, whereas *in utero* life, childhood and adolescence probably represent periods of greater impact of nutritional factors that may be involved in cancer. Some data strongly suggest that diet during early age and during pregnancy may have an impact on cancer incidence during adulthood (Vatten et al., 2005). Nutrition (daily intake of calories) has a major impact on the secretion of several pituitary hormones, such as a growth factor which, in turn, strongly influences cell proliferation in specific tissues. Since 1950, the height of girls and boys in France and most other industrialized countries has dramatically increased (by over 10 cm in young adult age), as has their foot size; moreover the mean age at menarche has decreased by 2 to 3 years. In countries where diet is poor in protein or in calories, or where intestinal parasites are common, the height of children and adolescents is generally much smaller than in industrialized or affluent countries and varies with the socio-economic class; in these countries the incidence of breast and colon cancer is also much lower. When people migrate from these regions to developed countries (or when their lifestyle is "westernized", as in Singapore), their height increases, menarche occurs earlier and the incidence of breast and colon cancer rises. It has been hypothesized that these changes may be related to variations in hormonal balance. High levels of IGF1 and IGF2 are associated with higher incidence of breast and colorectal cancer (Hankinson et al., 1998; Khandwala et al., 2000; Schneid et al., 1992). Thus a high incidence of these types of cancer and higher height and early age at menarche might be related to higher levels of growth factors.

(ii) It is plausible that the effects of nutrition on cancer are exerted by unspecific factors such as the amount of calories, rather than by specific nutrients or foods (Elias et al., 2007; Kolaja et al., 1996; Roe, 1979). Animal experiments consistently show that total energy intake has more influence on

cancer occurrence than specific nutrients. In such experiments, notably in rodents, higher daily food intake is associated with shorter life expectancy and higher cancer incidence. The biological rationale behind the total energy hypothesis comes from the known link between mitotic activity and cancers of epithelial origin (e.g., colorectal cancer), and between high energy intake and mitotic activity (e.g., in the colon). In humans, overweight and obesity are also associated with increased cancer incidence, but we do not know whether or to what extent an increase in daily food intake has an impact on cancer incidence. The protective role of physical activity on colorectal and breast cancer is independent of weight (IARC, 2002) and could be related to biological mechanisms that are also influenced by energy intake. Daily food intake varies markedly from country to country; in France it has markedly increased during the past decade (even in individuals without overweight). The average daily food intake in France is now 3500 kcal/day/inhabitant. The average in developed countries is 3300 and in developing countries 2400, but it can be much lower in some countries, for example 1600 in Ethiopia. The impact of these variations of food intake on cancer incidence in humans has not yet been adequately studied.

(iii) Another new research avenue concerns the concept of "nutritional disequilibrium". Up to now, most studies have assessed cancer risk by comparing subjects having minimal, intermediate and maximal intake of nutrients. Nutritional disequilibrium is more concerned with the "best balance" between several nutrients, without reference to either too low or too high quantities of a given nutrient. The quality of the mix between nutrients could be the critical factor, instead of quantitative intake of specific nutrients.

6. Possible causes for underestimation of cancers associated with non-hereditary risk factors

6-1 Underestimation of the role of infectious agents

That infectious agents play a role in cancer occurrence has been known for over 40 years, and research on viruses and cancer has led to the unveiling of many basic biological mechanisms implicated in normal life and in carcinogenesis.

Many cancers are associated with viral, bacterial and parasitic agents. Some infectious agents are now known to be a necessary cause of a cancer, such as human papillomavirus (HPV) in cervical cancer. Occurrence of several other cancers is strongly related to infectious agents, e.g., *Helicobacter pylori* colonization for stomach cancer, chronic infection with hepatitis B and C viruses (HBV and HCV) for liver carcinoma, EBV for Hodgkin disease, and various viruses for some leukaemias.

Furthermore, cancers found with greater frequency in HIV-positive patients not treated with highly active antiretroviral agents (HAAR therapy) (e.g., Kaposi sarcoma and non-Hodgkin lymphoma (NHL)) show that some immune disorders associated with infections could be at the origin of several types of cancer. This hypothesis may also have a role in NHL and leukaemia occurring in HIV-negative subjects, who may have a genetic propensity to develop a cancer when infected with as yet unidentified infectious agents (Zur Hausen, 2006).

More and more epidemiological and laboratory data suggest that infectious agents may be direct or indirect causes of various cancers, including HPV in squamous carcinoma of the aerodigestive tract (Hammarstedt et al., 2006).

Infections could influence cancer occurrence through inflammatory processes that would have an impact on immune function and change the likelihood of developing cancer. Similar mechanisms could underlie the effect of agents acting on inflammatory processes to modify the likelihood of cancer, e.g., the anticancer effect of non-steroidal anti-inflammatory drugs, and the role of steroid hormones in endometrial cancer (Modugno et al., 2005).

Hence, it is expected that following further research, the proportion of cancer attributable to infectious agents will substantially increase.

6-2 Poor knowledge of the role of hormone-related factors

There is now consistent evidence that in women, hormones involved in reproductive function are implicated in breast and in gynaecological cancers (Rochefort, 2007). The reproductive function involves several hormones and much remains to be elucidated regarding their role in cancer; for instance, in breast

cancer, the respective roles of steroid hormones such as estrogenic, progesteronic and androgenic hormones, and of polypeptide hormones such as the growth hormone and prolactin remain to be clarified. While lifetime exposure to steroid hormones might promote breast cancer development, prolactin could represent a strong protective factor. Furthermore, peptide hormones and receptors involved in obesity and diabetes mellitus, but also in growth, could be far more efficient than steroid hormones for transformation of normal breast epithelial cells into cancerous cells of high malignant potential.

In spite of many gaps in knowledge, research on breast cancer has permitted a better understanding of the relationship between hormones and cancer and led to the discovery of efficient hormonal treatments (e.g., tamoxifen) (Rochefort, 2007). It is also hoped that breast cancer research will lead to the discovery of drugs for chemoprevention of the disease in healthy women.

6-3 Difficulty in assessing exposures accurately and the "risk dilution" or "misclassification" effect

Retrospective assessment of exposure in case–control epidemiological studies is often imperfect because most information provided by individuals is prone to bias (recall, interview, selection biases, etc.). Information from laboratory measurements in humans often focuses on one or few biological items that are not too difficult or expensive to measure. Use of past medical records is often limited by a lack of standardization of the data recorded.

Imperfections in exposure assessment generally lead to "misclassification" of an exposure–disease assessment[1], which results in finding increased (enhancing effect) or decreased (protective effect) risks of smaller magnitude (i.e., RR closer to unity (1.0)) than if perfect exposure measurement had been possible. Furthermore, most human cancers are not due to a single agent but to simultaneous or consecutive combinations of several agents (including complex mixtures) and epidemiological methods have poor ability to explore the effect of such mixtures.

There is clearly a need for some sort of "exposome" that could provide unbiased information on many exposures at the same time, incorporating the quality and quantity of exposures, and time relationships between exposures (Wild, 2005). Such an "exposome" would usefully supplement new laboratory analytical methods that screen DNA alterations (e.g., mutations) and variations (e.g., single nucleotide polymorphisms, SNPs), and phenomena occurring at epigenetic, proteinic and metabolic levels. For example, in the case of ionizing radiation, the study of aberrations in blood lymphocytes provides useful information regarding exposure (see Miller et al., 2001 for other examples). In that respect, there is a need to search for biomarkers that could (i) measure exposures, and (ii) identify individuals with biological characteristics making them more susceptible to cancer.

6-4 Difficulty in performing studies in children and adolescents

Most of what we know about the causes of cancer has been derived from studies in adults. However, research has gradually revealed that younger age and even *in utero* life is a period of higher susceptibility to carcinogens that has considerable repercussions on cancer occurrence during adulthood. This phenomenon was first recognized for ionizing radiation, and later for ultraviolet radiation and some medicinal products (e.g., diethylstilbestrol, DES). It is now suspected that the initial steps of some cancers may take place *in utero* or during the first years of life (e.g., testis cancer, cutaneous melanoma, some breast cancers). Infancy, childhood and adolescence seem pivotal for hormone-related cancers (e.g., breast, ovary, prostate) and probably also for cancers influenced by dietary habits (e.g., colorectal cancer and stomach cancer). A relationship has been observed between the size of the newborn and probability of breast cancer, suggesting the impact of *in utero* hormonal influence (Vatten et al., 2005).

Epidemiological research in minors poses considerable problems. The identification of suitable controls may be more problematic than with adults and in many countries the impossibility of collecting biological material (e.g., blood samples) from children or adolescents poses major limits on the scope of possible investigations. In addition, childhood exposure is difficult to assess both in retrospective

[1] Sometimes also called «dilution» of exposure-disease assesment.

studies (e.g., case–control studies) and in cancer-related prospective studies, because of the need for very long follow-up. Furthermore, numerous legal, moral and ethical barriers discourage the initiation of studies in children and when possible such studies are likely to be very expensive. Current developments in the legislative environment in North America and in Europe are further diminishing the prospects for conducting studies involving children. However, despite these difficulties and the very long timescale necessary for obtaining relevant information, cohort studies should be launched, because they would provide unique and important information.

7. Early detection and the emerging concept of "cancer without disease"

The availability of methods allowing detection of cancers at an earlier stage of development leads to substantial increases in cancer incidence. This increase is essentially due to the finding of cancers that cause no symptoms or clinical signs, that are more indolent and would probably never (or would take a long time to) become clinically apparent[2]. The issue of increased detection of tumours having histological characteristics of cancer, but not the clinical features of cancer, was already raised by Doll and Peto (Appendix C of their 1981 publication) and other authors (Fox, 1979).

In the past, many of these indolent tumours remained unidentified and never caused death. Thus their detection can be considered as an undesirable side-effect of screening. The treatment applied is often similar to that of potentially more dangerous cancers because, at present, it remains hard to predict the short-term or long-term outcome of small cancers on the basis of available clinical, histological, imaging and laboratory parameters. In this respect, the increase in cancer incidence and in overtreatment induced by early-detection methods may also be viewed as a consequence of the fact that diagnosis of cancer is based on histological criteria, rather than on criteria allowing prediction of the likely clinical course of the disease. Many of the small tumours would not evolve into invasive disease, i.e., they are "cancers without disease" (Folkman and Kalluri, 2004).

It remains to be determined whether indolent screen-detected cancers are associated with risk factors found to be associated with symptomatic or clinically apparent cancers. For several organs, the answer is likely to be negative. For instance, spontaneous formation of small tumours having cancerous histological characteristics takes place in the thyroid of many subjects (mainly in females), but most will never evolve into life-threatening disease. The spectacular increase in thyroid cancer incidence observed in many countries in the last decades parallels the advent of new exploratory tools, such as ultrasonography with high-frequency probes and fine needle biopsy methods, and does not seem to be related to changes in exposure to yet unknown risk factors. The clinical studies carried out for early detection and treatment of neuroblastoma in children have not resulted in lower mortality, which strongly suggests that most of these small screen-detected tumours would not have led to an invasive cancer (Schilling et al., 2002; Woods et al., 2002).

Another example is prostate cancer. Up to now, no consistent environmental or lifestyle risk factor has been definitely identified for this cancer and prostate cancer occurrence is largely associated with ageing. The incidence of prostate cancer has dramatically risen in populations where testing for prostate-specific antigen (PSA) has become widespread (See Section A2). Many of the prostate cancers found by PSA testing would have remained clinically silent, and probably most of these should not be associated with an environmental or lifestyle risk factor.

It is therefore possible to hypothesize that the net impact of early-detection methods increases the proportion of cancers for which there is no real environmental or lifestyle risk factor, so that the proportion of cancers for which such risk factors may account is decreased. In this respect, AFs estimated in this report are probably more valid for mortality data than for incidence data.

[2] In addition to indolent cancers, finding of in situ cancers is also considerably increased by early detection methods. These are tumours that have not developed beyond the basal membranes separating the epithelium from the conjunctival stroma. Before widespread availability of mammographic screening, in situ breast cancers represented less than 2% of all breast tumours, while they may now represent up to 20%. In situ cancers have low malignant potential, but in many organs, the likelihood of transformation into invasive cancer is uncertain, and therefore, treatment is often similar to that of invasive cancer. Note that regardless of malignant potential to evolve into an invasive cancer, some in situ tumours (e.g., in the breast) may be voluminous and require extensive surgery. Normally, cancer incidence data only include invasive cancers, and in situ cancers should not be counted as incident cancers. However, on needle biopsies, it can be difficult to distinguish in situ and invasive cancer in a small specimen of a small tumour.

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Section E2: General discussion

This study shows that in France, in the year 2000, tobacco smoking and alcohol drinking were by far the main risk factors of cancer; tobacco accounting for 27% of the total cancer burden in men and 6% in women, and alcohol accounting for 11% of the total burden in men and 4% in women. Infectious agents, obesity and overweight, physical inactivity, ultraviolet radiation, occupation and hormone treatment each accounted for 1 to 3.3% of the total cancer burden in men or in women. Reproductive factors and air, soil, food and water pollutants each accounted for between 0.1% and 1% of the total cancer burden. For pollutants, we considered only IARC Group 1 carcinogens. If suspected carcinogens such as outdoor air pollution with fine particles had been considered, pollutants could account for around 1% of all cancers.

This study was based on established carcinogenic agents (i.e., IARC Group 1 carcinogens), i.e., agents for which there is sufficient evidence for carcinogenicity in humans. Most relative risks were derived from the most recent meta-analyses of observational epidemiological studies. A few attributable fractions (AFs) were not derived from relative risks and data on exposure, but from AFs directly estimated for entire populations (i.e., those for sun exposure, EBV infections, and occupational asbestosis). A model approach was never used. We never had recourse to estimations based on expert opinion.

The AF estimates presented in this report are to be considered as minimal estimates, as we are aware that prevalence of some exposures may be underestimated (e.g., infections). In the absence of better scientifically valid sources of data, these remain the best estimates based on current scientific knowledge.

The study discarded numerous agents for which some scientific literature suggests that they are carcinogenic in humans. The basic rule is that only accumulation of scientific evidence from several sources (e.g., different independent scientific teams) and several disciplines (e.g., laboratory experiments and epidemiological data) can form the basis for a set of arguments consistent with the recognition of an agent as carcinogenic, or not carcinogenic, in humans.

Most studies on cancer risk factors were carried out in North America, the UK, the Nordic countries, the Netherlands, Italy or Asia. For many risk factors, no study has been conducted in France. This does not mean that relative risks derived from non-French studies are not valid for France, as toxic substances, drugs, pollutants, etc., are expected to exert similar effects in France and in other industrialized countries.

Weaknesses of this study reflect the currently inadequate knowledge in several fields, in particular:

1. The limited understanding of the complex processes involved in carcinogenesis (see Section E1).
2. The lack of reliable data on the causal association between many substances and cancer, bearing in mind that a statistical correlation between cancer and exposure to a substance does not imply causality.
3. Uncertainty about dose–effect relationships between exposure and cancer occurrence (see Section E1). The shape of the dose–effect relationship may be non-linear, e.g., an agent might be highly carcinogenic at high dose and innocuous at low dose.
4. The lack of availability of accurate data on exposure to known risk factors.
5. Differences in length of the lag-time for different carcinogens. For some factors, lag-time

may be very long (e.g., reproductive factors and breast cancer occurrence after 50 years old), but it may also be short, for instance benzene and leukaemia (about 5 years of lag-time).

Methodological limitations of the study

The methods we used for estimation of AFs may be criticized on several grounds:

(1) The lag-time of 15 years was somewhat arbitrary and exposures may have changed across generations. However, we adapted our choice of lag-time according to its relevance for risk factors. Thus, for instance, for hormone therapy and oral contraceptives, only current use was taken as relevant to breast cancer. For ultraviolet radiation and for professional exposure to asbestos, approaches for estimating AFs were not based on a lag-time.

(2) RRs and exposure measurements for AF calculations should be derived from similar populations having similar exposure to a specific risk factor. Since most of the RRs and data on exposure originated from different sources, the choice of RRs and exposures was sometimes not optimal (e.g., for physical inactivity).

(3) We assumed AFs to be equivalent for cancer incidence and mortality. This assumption is true only if the risk factor is not a prognostic factor for mortality, as the AF would then be different. For instance, obesity is a risk factor for breast cancer occurrence, but probably a stronger risk factor for breast cancer mortality after 50 years old. In this respect, the AF associated with obesity for breast cancer mortality is probably underestimated.

Difficulty in finding exposure data for France

We found exposure data for France for the majority of risk factors. However, we have to deplore the difficulty encountered in accessing many of the exposure data, despite the devoted efforts of the working group to identify potential sources. For some exposure prevalence data, reports or articles do not sufficiently describe the collection methods used and it therefore remains difficult to assess their quality. Many sources of data were not published in the scientific literature or in other peer-reviewed formats. This was particularly the case for data on occupational exposures. Great care was taken in choosing exposure data most representative of the prevailing situation in France at the end of the twentieth century. Data from certain sources were not used because they were derived from selected sub-populations unlikely to be representative of the French population. Exposure data doubtless exist of which we are unaware, but it is improbable that their availability would significantly change the estimates presented in this report.

In any case, this work has revealed the need for France to constitute a central repository of data on exposure prevalence, for instance, for the purpose of health surveillance. This repository should specify the methods used for data collection and be updated regularly.

How the study results can address public concerns about the "environment"

In the developed countries, exposure to known carcinogens has significantly decreased over time, mainly since the 1950s, as has exposure to many indicators of possible contact with carcinogens (e.g., some gases, "dirty" industrial activities, uncontrolled massive waste disposal). This historical fact in itself argues against the common perception that the "environment" is the cause of increases in cancer incidence.

For many exposures, there is not sufficient scientific evidence to establish them as cancer risk factors. In this respect, public concern about "environmental pollutants" is disproportionate to the known magnitude of impact of such pollutants on cancer. As stressed in the introduction to this report, some confusion comes from the different definitions for "environment", which has different meanings according to language. In their most appropriate sense, "environmental pollutants" include pollutants of water, air, soil and food.

Attribution of cancers with unknown cause to a single cause by default (or to a group of causes, e.g., "pollution") is unjustified and represents a fallacious argument. By similarly flawed reasoning, the gap in cancer causes could equally be attributed to global climate change, to the increasing number of televisions in our immediate environment, or to the

increase in social well-being.

It is unlikely that all cancers with 'unknown' cause are due to factors that will ever be identified. However, as seen in Sections A2, D3 and E1, even if we do not know the risk factor(s) responsible for the increasing incidence of a cancer, we usually do have clues as to the likely type of risk factor involved or not involved. In this respect, pollutants of air, food, water and soil, as well as occupational exposures, do not provide the preferred working hypotheses for the identification of risk factors responsible for the increase in incidence of some cancers. The development of new detection methods, screening effects, lifestyle factors, diet during pregnancy, infancy and childhood and hormonal and infectious agents are stronger avenues for future research.

Past studies on attributable risk of cancers

Several studies that estimated proportions of cancer attributable to risk factors were restricted to one risk factor or to one particular site of cancer (e.g., Mezzetti et al., 1998). Only four studies other than the present one estimated the impact of carcinogens on large populations and they used quite different methodologies (Doll and Peto, 1981; Olsen et al., 1997; Danaei et al., 2005; Doll and Peto, 2005). The main results of these studies are summarized in Table E2.1.

The first estimate of the relative importance of genetic and environmental factors in the global burden of cancer was made by Doll and Peto (1981) using cancer mortality data from the USA. In their seminal work, these authors came to the conclusion that around 80% of cancers could be attributable to a specific lifestyle or known environmental cause (Table E2.1). Subsequently, R. Peto and co-workers applied the same method to estimate the impact of tobacco smoking on the worldwide burden of cancer (Peto et al., 1994). Recently, J. Peto updated the estimates of the relative importance of causes of cancer for the world (Peto, 2001).

In 1981, Doll and Peto postulated that the greatest differences in cancer mortality between countries could reveal the pressure of environmental and lifestyle factors on cancer burden. Countries with the lowest rates for a specific cancer were more likely to reflect the background cancer rate essentially attributable to genetic or other endogenous factors. Their ranges of "acceptable estimates" (Table E2.1) were quite wide, reflecting uncertainties in the estimates. Thus, for instance, diet was deemed to account for 35% of cancer mortality, but the range of acceptable estimates was 10 to 70%. These estimates reflected the quality of the data available at that time. Furthermore, this methodology was implicitly based on the assumption that each type of cancer can be considered independently. This assumption is open to discussion. One factor, such as a high calorie intake through food, may increase the incidence of some cancers (directly or by increasing some hormonal secretions) and decrease the incidence of others (by enhancing the organism's defences). This is why it is useful to consider the overall impact of each risk factor. Another assumption was that non-genetic causes would sooner or later be identified for most common cancers. Nowadays, this assumption is no longer regarded as valid and it appears that the occurrence of many cancers is probably not associated with lifestyle or environmental causes (e.g., most prostate cancers) (see Section E1).

In 2005, Doll and Peto produced new estimates of the proportions of cancer deaths attributable to environmental and behavioural risk factors, this time for cancer deaths in the United Kingdom (Table E2.1). As for the 1981 report, the methods used to estimate AFs were not clearly detailed (e.g., sources of relative risks, exposure prevalence data, comparisons of cancer death rates in populations exposed and non-exposed to cancer risk factors). However, comparison of the figures reported in the two publications by Doll and Peto shows substantial changes in AF estimates for several factors, for instance diet. An accompanying note in the 2005 publication said that probably only 2% is avoidable in practice, mainly through avoidance of obesity. The AF for occupation was halved, probably to reflect changes in professional environments towards cleaner working places and less contact with hazardous substances.

Researchers from the Harvard School of Public Health (Danaei et al., 2005) attempted to determine the proportion of cancers attributable to lifestyle and environmental factors worldwide. These authors used estimates of relative risks derived from systematic reviews and meta-analyses. Exposure prevalences were estimated for each World Bank Region. For high-income countries, eight cancer risk factors were selected, and important risk factors such as

reproductive factors were not taken into account. Selection of exposure prevalence data did not always pick up the most appropriate and reliable sources in countries categorized as "high-income countries". The referent category for "no exposure" was chosen as the "theoretical minimum risk exposure distribution", an arbitrary category that seldom corresponds to real-world conditions. The authors concluded that the nine factors they selected accounted for about 43% of cancer deaths in high-resource countries in 2001.

The studies by Doll and Peto (1981, 2005) and by Danaei et al. (2005) were helpful for estimating the global effects of the main established causes of cancer. But these approaches were not always based on data on prevalence of exposure of populations (or of population subgroups) to known risk factors derived from, for instance, nationwide surveys or exposure monitoring. Furthermore, standard definitions of risk factors were not implemented across countries. Finally, the selection of risk factors in these studies was based on expert opinion rather than on attempts to systematically include all relevant cancer risk factors.

A study in the Nordic countries systematically examined prevalence of exposure to established risk factors in each Nordic country (Denmark, Finland, Iceland, Norway and Sweden) and then summed the estimates for all five countries, after weighting for population (Olsen et al., 1997). The relative risks used were derived from studies conducted in Nordic countries or, if no such study existed, from meta-analyses or the best available studies. In this respect, the methods used by the Nordic study resemble the approach we used for France. However, the Nordic study did not include several risk factors such as hormone replacement therapy, because in the mid 1990s the association between use of hormone replacement therapy and cancer had not yet been properly assessed by epidemiological studies or randomized trials. The same applies to physical inactivity.

Compared with similar previous work, our report provides new and more detailed information. Selection of risk factors was based on the best available knowledge of cancer risk factors in the year 2007 (and not on expert opinion), and exposure prevalences were derived from the most relevant French sources of data. However, further progress is still possible and relevant research is encouraged.

In spite of the different methodological approaches, many conclusions of the three studies based on selection of established cancer risk factors and estimates of prevalence of exposures (Olsen et al., 1997; Danaei et al., 2005; Tubiana et al., 2007) are consistent on several points:

(i) Tobacco smoking remains by far the main exogenous cancer risk factor, followed by alcohol drinking. The differences between the three studies on attributable fraction for tobacco are mainly due to differences in smoking prevalence between countries.

(ii) Two studies (Olsen et al., 1997; this study did not produce estimates of attributable fraction for dietary factors, and one (Danaei et al., 2005) just selected low intake of fruit and vegetables. As a result, at best only a marginal number of cancers, in the range of 0 to 3% were attributed to dietary factors.

(iii) The causes of large proportions of cancers are unknown and may be endogenous factors without significant impact of exogenous factors,

(iv) The impact of occupational risk factors is small and probably has diminished over recent decades; efforts should continue to further reduce this,

(v) Environmental pollution appears to be a relatively small risk factor. This does not mean that it should be neglected or overlooked. Rather, further fundamental and epidemiological research should be pursued on air, soil, food and water pollutants, with more thorough examination of defence against carcinogenesis and dose–carcinogenic effect relationships.

(vi) Finally, it appears that our knowledge on infectious factors (mainly viral) is insufficient.

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Table E2.1 - Number of cancer cases or of cancer deaths and proportions attributed to various factors since the seminal work of R Doll and R Peto in 1981 *

	Doll and Peto, 1981, USA		Olsen et al, 1997, Nordic countries		Doll and Peto, 2005, UK		Danaei et al, 2005, high-income countries	This report		
Risk factors	% of cancer deaths	Range of estimates	% of cancer cases in men	% of cancer cases in women	% of cancer deaths	Range of estimates	% of cancer deaths	% of cancer deaths in men	% of cancer deaths in women	% of cancer deaths
Tobacco	30	25-40	19	9	30	27-33	29	33,4	9,6	23,9
Alcohol	3	2-4	2	1	6	4-8	4	9,4	3	6,9
Infectious agents	10?	1-?	2#	3#	5	4-15	<1.5 ∫	3,3	4,4	3,7
Diet	35	10-70	?§	?§	25	15-35	3 Ψ	NI	NI	NI
Obesity and overweight			<1	1			3	1,2	2,3	1,6
Physical inactivity			NI	NI	<1	0-1	2	0,5	3,2	1,6
Occupation	4	2-8	3	<1	2	1-5	NI	3,7	0,5	2,4
Pollutants	2	<1-5	<1 II	<1 II	2	1-5	NI	0.04	0,3	0,1
Urban air pollution			NI	NI			1	NI	NI	NI
Industrial products	<1†	<1-5	NI	NI	NI	NI	NI	NI	NI	NI
Food additives	<1	0.5-2	NI	NI	NI	NI	NI	NI	NI	NI
Medicines and medical procedures	1**	0.5-3	NI	NI	<1	0-1	NI	NI	NI	NI
Hormone replacement therapy and oral contraceptives			NI	NI			NI	NI	2,2	0,9
Reproductive factors	7 ϴ	1-13	NI	NI	15	10-20	NI	NI	1,1	0,4
Non-medical ionizing radiation	3‡	2-4	<1¶	<1¶	4	3-5	NI	NI	NI	NI
Ultraviolet light			4	5	1	1	NI	0,6	0,9	0,7
Man-made ionizing radiation	NI Я	NI	2	3	<1	<1-1	NI	NI	NI	NI

NI: factor not considered as being a cancer risk factor by the study - * Figures, ranges and «?» in the Table are as reported in the original publication
** Includes medical radiation, chemotherapeutic agents, oral contraceptives, hormone replacement therapy - † Includes numerous chemicals and physical agents introduced in daily life by modern industry
‡ Called «geophysical factors in Doll et Peto 1981», and included non-medical ionizing radiation and ultraviolet light
§ Authors considered that insufficient evidence existed for calculation of an attributable fraction - II Restricted to passive smoking - ¶ Restricted to radon - # Restricted to *H. pylori* infections
∫ Restricted to unsafe sex (1%) and contaminated injections in health-care settings (<0.5%) - Ψ Low fruit and vegetable intake - Я Included in the category «Medicines and medical procedures»
ϴ Includes sexual behaviours, i.e., infectious agents implicated in cancer of the cervix uteri

Section E3 : Recommendations

The conclusion that only a fraction of cancers occurring today in France is attributable to specific causes (and therefore is theoretically preventable) stresses the limitations of current knowledge on human carcinogenesis. While it is expected that in the future the evidence in favor or against a role of other risk factors will accumulate and eventually contribute to elucidating their contribution to human cancer, recommendations can be formulated to improve this process.

1. Recommendations to the scientific community

1.1 There is a need for large-scale, long-term prospective studies on exogenous and endogenous risk factors of cancer and other chronic diseases, with repeated measurements of relevant exposures. While the establishment and conduct of such studies exceed the resources of individual research groups, the medical research community should be encouraged to coordinate itself towards this goal. Links should be fostered between epidemiological and biological research. In the design and interpretation of epidemiological studies, more cooperation is recommended between epidemiologists, biologists, and clinicians. Cancer registries should be better used for cancer research; they should be encouraged to collect data regarding tumour characteristics as well as basic information (e.g., occupation) on the patients.

1.2 More attention should be paid to the assessment of pre- and peri-natal exposures, and of those occurring in infancy, childhood and adolescence. Ideally, the effects of these exposures should be studied within the framework of prospective studies (see recommendation 1.1); development of intermediate markers of risk might reduce the need for long-term follow-up.

1.3 The areas of cancer research which should be given the highest priority to improve the current understanding of the causes of human cancers – and the ability to prevent them – are those on nutrition, hormones, and infectious agents. The key contribution is likely to come from the development and validation of sensitive and specific methods of exposure assessment, including biomarkers, to be applied to large-scale population studies. Intervention studies would also provide critical evidence in the field of nutrition and cancer.

1.4 For known and suspected carcinogens, priority should be given to research (based on both epidemiological or biomarker approaches) aimed at analyzing defenses against mutation at the cellular level and against mutant cells at the tissue and organism levels.

1.5 In reviewing and quantifying the contribution of different causes to human cancers, more weight should be given to evidence-based summaries of the available data, than to the results of individual studies. The highest degree of scientific rigor and consistency should be applied to the assessment of available data. In general, conservative estimates are preferable to inferences based on weak evidence. Conflicts of interest of reviewers should be declared.

1.6 Publication bias should be avoided. A registry of all epidemiological studies (or at least all long-term prospective studies) should be set up and all results (positive or negative) should be collected. Leading journals should accept the publication of only studies which have been registered.

2. Recommendations to the administration and national or international research foundations

2.1 Ambitious long term studies should be encouraged. In particular, cohort studies should be set up, following individuals from the beginning of their life in utero to 50 or 60 years old in order to better understand the factors which influence health.

2.2 Data on cancer incidence should be collected from cancer registries, checked and made available to the research community in a timely manner. In normal circumstances, a delay of more than three years should not be accepted. In France, in the context of the 2003-2007 Cancer Plan, the surveillance system of the population has been improved, involving several institutions such as InVS, INSERM, AFFSET, INCa which are in charge of the collection and interpretation of data. Strong cooperation between these agencies is recommended in order to set up a database that would be constantly and rapidly updated and which would facilitate multidisciplinary research at the national, European and international level.

2.3 Large-scale, high-quality cross-sectional studies should be promoted to assess exposure to known and suspected cancer risk factors. Such surveys should be repeated at regular intervals. If already in place, these surveys should be coordinated and their results made easily accessible to the research community.

2.4 Priority should be given to the support of large-scale, prospective studies of cancer risk factors (see recommendations 1.1 and 2.1). Novel funding mechanisms might be taken in consideration to support such long term projects.

3. Recommendations regarding the information to the general public and the media

3.1 Emphasis should be given to comprehensive and evidence-based reviews of the evidence on the causes of human cancers. Evaluations made by international, multi-disciplinary panels should be given more weight.

3.2 Specific aspects of cancer risks and determinants (e.g., one particular cancer, one subset of the population, one risk factor) should be considered in a general perspective (e.g., mortality from all cancers, major risk factors) rather than in isolation. The role of chance and bias in generating false positive and false negative results should be given proper consideration.

3.3 The general public should be educated to cancer risk assessment and management. In particular, it is important that lay individuals acquire the ability to critically evaluate results on cancer risk factors. Health education at school offers the greatest opportunity for such educational efforts.